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Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 28, 30-46, 48-66, and 68-83 are pending in the application, with 28, 46, and 66 being the independent claims. Claims 28, 47 and 67 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. This amendment is made to cancel claims and present the rejected claims in better condition for allowance by adding the limitations of dependent claims into the independent claims. Applicants submit that a new search is not required as none of the limitations are new, no claims have been added, and new issues have not been raised. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 28, 46, 66, and their dependents were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being indefinite in the recitation of the phrase "ability to interfere." The Examiner alleged that the phrase is relative to the degree of interference of the test compound. Applicants respectfully traverse this rejection as it may apply to the amended claims.

Without acquiescing to the rejection and solely to advance prosecution, claims 28 and 46 were amended to recite "comparing the level of multiubiquitin chains formed in the presence of said test compound to the level of multiubiquitin chains formed in the absence of said test compound." One of ordinary skill in the art would readily be able to determine if a test compound inhibits the ubiquitination reaction mediated by the Anaphase Promoting Complex (APC) by comparing the level of multiubiquitin chains formed in the presence of the test compound to the level of multiubiquitin chains formed in the absence of said test compound. If the level is higher in the absence of the test compound, the test compound can be considered an inhibitor. Assays for the measurement of the levels of multiubiquitin chains formed are provided in the specification, *e.g.* paragraph [0066], and may also be found in the art.

The same argument applies to claim 64, which was amended, without acquiescing to the rejection and solely to advance prosecution, to recite "comparing the level of ubiquitination of APC11 in the presence of said test compound to the level of ubiquitination of APC11 in the absence of said test compound." As a person of ordinary skill in the art would clearly understand how to identify inhibitors of APC-mediated ubiquitination reactions using the comparison set forth in the claims, Applicants respectfully request that the rejection be withdrawn.

Claims 28-83 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being incomplete for omitting essential claims. The Examiner alleged that essential reaction components were omitted, specifically E1, E2, and ATP. Applicants respectfully traverse this rejection as it may apply to the amended claims.

Solely to advance prosecution and without acquiescing to the rejection, claims 28, 46 and 66 were amended to recite E1, E2, and ATP. As the elements outlined by the Exmaminer are now incorporated into the rejected claims, Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 28-33, 35, 39-41, 46-53, 55, and 59-61 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kirschner *et al.* in view of Lorick *et al.*, Zachariae *et al.*, Gonen *et al.*, and Hatfield *et al.* Specifically, the Examiner alleged that Kirschner *et al.* teaches an assay for inhibitors of ubiquitination reaction utilizing E1, E2, ATP, APC2 and APC6, but acknowledges that APC11 is not disclosed, nor the use of specific E1 or E2 enzymes. The Examiner alleged that Lorick *et al.* describes that RING finger motif-containing E3s are essential for E2-dependent ubiquitination and identify APC11 as containing a RING finger. The Examiner further alleged that Zacharie *et al.* teaches that APC11 is a vital component of the APC system, and that both Gonen *et al.* and Hatfield *et al.* disclose UBCH5b and UBA1. Applicants respectfully traverse this rejection as it may apply to the amended claims.

Claims 28-33, 35, 39-41, 46-53, 55, and 59-61 are drawn to methods for screening for substances that inhibit the ubiquitination reaction mediated by APC11 in the absence of other APC subunits. *In re Vaeck* (947F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)), outlines the factors required for establishing a *prima facie* case for obviousness: prior art references that teach all claim limitations, a motivation to combine the references in the references themselves or knowledge known to a person of skill in

the art at the time the invention was made, and a reasonable expectation of success from the combined elements in the references. As discussed below, Applicants respectfully assert that these requirements have not been met to support a *prima facie* argument for obviousness for the amended claims.

The cited references do not contain every limitation of the claims.

The combination of references cited by the Examiner does not teach the use of APC11 without other APC subunits as in the claimed method. Kirschner *et al.* discloses a "mitotic destruction complex" including CDC27 and CDC16, with no mention of APC11, for ubiquitinating substrates (*see* Kirschner *et al.*, page 4, lines 31-35). Lorick *et al.* discloses the use of a novel RING finger protein, AO7, in E2-dependent ubiquitination and speculates as to whether other RING finger proteins may be important for E2-dependent ubiquitination. Lorick *et al.* notes that the anaphase promoting complex is an E3 (p. 11364, first column, last full paragraph). Lorick *et al.* further notes that APC11p is an example of a RING included in protein complexes that function as E3s and speculates that additional RING-containing proteins "will eventually be found to be E3 components" (page 113688, first paragraph under "DISCUSSION"). Nowhere does Lorick *et al.* teach or suggest that APC11 is not only required for APC-mediated ubiquitination, but is also *sufficient* for mediating ubiquitination in the absence of other APC subunits. Instead, Lorick *et al.* clearly identifies APC11 as an important part of the complex.

Zachariae *et al.*, a 1999 review article summarizing the field of APC, does not remedy this deficiency as it likens APC to SCF, an E3 described therein in having at least

four required subunits, including the RING-containing Hrt1 subunit. In this comparison, Zachariae *et al.* suggests that the APC2, a cullin-like subunit of APC, is important for bringing substrates in contact with APC, and states APC11 interacts directly with APC2 (page 2042, last paragraph). Indeed, Zachariae *et al.* goes on to say that APC2 and APC11 are APC subunits intimately involved in the catalytic activity of APC (page 2043, last paragraph). Figure 2 on page 2043 describes the theory presented by Zachariae *et al.* wherein a cullin (APC2) and RING protein (APC11) are required for E3 activity. Clearly Zachariae *et al.* indicates the importance of APC2 and does not teach the sufficiency of APC11 without other subunits to mediate ubiquitination.

As Gonen *et al.* and Hatfield *et al.* do not discuss APC11 at all, neither can teach that APC11 is sufficient to mediate APC-dependent ubiquitination. Therefore, none of the references, combined or alone, teach the use of APC11 in the absence of other APC subunits in the assay of the claimed invention.

There is no expectation of success

A person of ordinary skill in the art upon reading the cited art would have no expectation of successfully developing the claimed method of the present invention. The Examiner alleged that the cited references, especially Lorick *et al.* and Zachariae *et al.*, show APC11 to be "vital" to the APC-mediated ubiquitination reaction, and therefore the combination of APC11, UBA1, UBCH5b, ATP and ubiquitin would be expected to be able to ubiquitinate a substrate. For all the reason stated *supra*, none of the references suggests that APC11 in the absence of other APC subunits can mediate ubiquitination. Instead, the references suggest that other subunits are required. Therefore, one of skill in

the art would not reasonably have any expectation of success based on the art cited by the Examiner or known at the time of filing.

There is no motivation to combine the cited references

One of ordinary skill in the art would not have been motivated to combine the cited references upon reading them as there is no suggestion to do so. The Examiner alleged that one would be motivated to combine Lorick *et al.* with Zachariae *et al.* and Kirschner *et al.* as they all mention APC. However, one of ordinary skill in the art would not have been motivated to combine APC11 alone without other APC subunits with the elements of the claimed method as Zachariae *et al.* describes the importance of APC2 in the ubiquitination process, and Kirschner *et al.* specifically uses different subunits, namely the CDC27 and CDC16 proteins. Lorick *et al.* mentions APC11 in the context of being important in the APC complex and does not suggest that APC11 alone would be functional. Further, Hatfield *et al.* and Gonen *et al.* disclose the identification of an E1 and E2 from different organisms and systems, wheat and NF-κB respectively. Neither suggest the use of either component in the APC ubiquitination system.

For the reasons stated above, Applicants believe that a *prima facie* case for obviousness has not been established for the claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Priority

The Examiner acknowledged Applicants' claim for foreign priority based on EP 00113832.0, filed June 29, 2000, but notes that a certified copy of the application was not

filed. Applicants respectfully draw the Examiner's attention to the certified copy that was filed with the instant application on June 29, 2001.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 29, 47, 67 were cancelled.

28. (once amended) A method for identifying a compound that inhibits the ubiquitination reaction mediated by the Anaphase Promoting Complex (APC), comprising

(a) reacting APC11, ubiquitin, a ubiquitin activating enzyme (E1), a ubiquitin conjugating enzyme (E2), ATP, and a test compound under conditions and duration of time sufficient to obtain a measurable level of multiubiquitin chains in the absence of said test compound; and

(b) [determining said test compound's ability to interfere with the formation of multiubiquitin chains by APC11] comparing the level of multiubiquitin chains formed in the presence of said test compound to the level of multiubiquitin chains formed in the absence of said test compound;

wherein said reaction is made in the absence of APC subunits other than APC11.

30. (once amended) The method of claim [29] 28, wherein said APC11 is human.

31. (once amended) The method of claim [29] 28, wherein said E1 is wheat UBA1.

32. (once amended) The method of claim [29] 28, wherein said E2 is the human variant UBCH5b.

33. (once amended) The method of claim [29] 28, wherein the formation of multiubiquitin chains is measured using an antibody.

38. (once amended) The method of claim [29] 28, wherein said formation of multiubiquitin chains is measured using fluorescence resonance energy transfer (FRET).

39. (once amended) The method of claim [29] 28, wherein one or more assay component selected from the group consisting of APC11, E1, E2 and ubiquitin is fused to an affinity tag.

46. (once amended) A method for identifying a compound that inhibits the ubiquitination reaction mediated by the Anaphase Promoting Complex (APC), comprising

(a) reacting APC11, ubiquitin, an APC substrate, a ubiquitin activating enzyme (E1), a ubiquitin conjugating enzyme (E2), ATP, and a test compound under conditions and duration of time sufficient to obtain a measurable level of multiubiquitin chains on said substrate in the absence of said test compound; and

(b) [determining said test compound's ability to interfere with the formation of multiubiquitin chains on said substrate by APC11] comparing the level of

multiubiquitin chains formed in the presence of said test compound to the level of multiubiquitin chains formed in the absence of said test compound;

wherein said reaction is made in the absence of APC subunits other than APC11.

48. (once amended) The method of claim [47] 46, wherein said APC11 is human.

49. (once amended) The method of claim [47] 46, wherein said APC substrate is CyclinB.

50. (once amended) The method of claim [47] 46, wherein said APC substrate is Securin.

51. (once amended) The method of claim [47] 46, wherein said E1 is wheat UBA1.

52. (once amended) The method of claim [47] 46, wherein said E2 is the human variant UBCH5b.

53. (once amended) The method of claim [47] 46, wherein the formation of multiubiquitin chains is measured using an antibody.

58. (once amended) The method of claim [47] 46, wherein said formation of multiubiquitin chains is measured using fluorescence resonance energy transfer (FRET).

59. (once amended) The method of claim [47] 46, wherein one or more assay component selected from the group consisting of APC11, E1, E2 and ubiquitin is a fused to an affinity tag.

66. (once amended) A method for identifying a compound that inhibits the self-ubiquitination reaction mediated by the Anaphase Promoting Complex (APC), comprising

(a) reacting APC11, ubiquitin, a ubiquitin activating enzyme (E1), a ubiquitin conjugating enzyme (E2), ATP, and a test compound under conditions and duration of time sufficient to obtain a measurable level of ubiquitination of APC11 in the absence of said test compound; and

(b) [determining said test compound's ability to interfere with the ubiquitination of APC11] comparing the level of ubiquitination of APC11 in the presence of said test compound to the level of ubiquitination of APC11 in the absence of said test compound.

68. (once amended) The method of claim [67] 66, wherein said APC11 is human.

69. (once amended) The method of claim [67] 66, wherein said E1 is wheat UBA1.

70. (once amended) The method of claim [67] 66, wherein said E2 is the human variant UBCH5b.

71. (once amended) The method of claim [67] 66, wherein said ubiquitination of APC11 is measured using an antibody.

76. (once amended) The method of claim [67] 66, wherein said formation of multiubiquitin chains is measured using fluorescence resonance energy transfer (FRET).

77. (once amended) The method of claim [67] 66, wherein one or more assay component selected from the group consisting of APC11, E1, E2 and ubiquitin is a fused to an affinity tag.